

BMJ Open Protocol for Compass: a randomised controlled trial of primary HPV testing versus cytology screening for cervical cancer in HPV-unvaccinated and vaccinated women aged 25–69 years living in Australia

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ABSTRACT

Introduction Australia's National Cervical Screening Program (NCSP) currently recommends 2-year cytology in women aged 18–69 years. Following a review of the NCSP prompted by the implementation of human papillomavirus (HPV) vaccination, the programme will transition in 2017 to 5-year primary HPV screening with partial genotyping for HPV16/18 in women aged 25–74 years. Compass is a sentinel experience for the renewed NCSP and the first prospectively randomised trial of primary HPV screening compared with cytology to be conducted in a population with high uptake of HPV vaccination. This protocol describes the main Compass trial, which commenced after a pilot study of ~5000 women completed recruitment.

Methods and analysis Women aged 25–69 years will be randomised at a 1:2 allocation to (1) 2.5-year image-read, liquid-based cytology (LBC) screening with HPV triage of low-grade smears (active control Arm A) or (2) 5-year HPV screening with partial genotyping and referral of HPV16/18-positive women to colposcopy (intervention Arm B). Women in Arm B positive for other oncogenic HPV (not 16/18) will undergo secondary randomisation at a 1:1 allocation to either LBC or dual-stained (p16^{INK4a} and Ki-67) cytology testing (dual-stained cytology). The primary outcome is cumulative CIN3+ (CIN3, adenocarcinoma in situ and invasive cervical cancer) following a 5-year HPV exit testing round in both arms, in women randomised to the HPV arm versus women randomised to the LBC arm, based on an intention-to-treat analysis. The primary outcome will first be tested for non-inferiority and if declared, the primary outcome will be tested for superiority. A total of 36 300 women in birth cohorts not offered vaccination and 84 700 women in cohorts offered vaccination will be recruited, bringing the final sample size to 121 000. The trial is powered for the secondary outcome of cumulative CIN3+ in screen-negative women, adjusted for censoring after CIN2+ treatment and hysterectomy.

Ethics and dissemination Approved by the Bellberry Ethics Committee (2014-11-592). Findings will be reported in peer-reviewed journals and presented at scientific meetings.

Trial registration number NCT02328872; Pre-results.

Strengths and limitations of this study

- This study is a large-scale, randomised trial of primary human papillomavirus (HPV) testing in the first country to implement a national publicly funded HPV vaccination programme, powered to detect cumulative CIN3+ at 5 years in screen-negative women; for the first time this outcome will be assessed in HPV-screened versus cytology-screened women within a cohort that was offered vaccination.
- The study is implemented within the National Cervical Screening Program in Australia, and the study will provide a sentinel experience of a 'real world' HPV screening programme.
- Secondary randomisation will assess the incremental benefits of a new technology for triage testing, dual-stained cytology, against liquid-based cytology, for triage of women with other oncogenic (not HPV16/18) types.
- The protocol for primary HPV screening involves the use of next-generation HPV testing platforms which perform partial genotyping—this is expected to improve the overall performance of HPV testing, but these platforms may not be universally used in all countries.
- The protocol for cytology screening in the active control arm involves the use of HPV triage testing with partial genotyping. This protocol is unlikely to be available in all countries still performing cytology.

INTRODUCTION

Australia will be one of the first countries in the world to transition from cytology-based screening to primary human papillomavirus (HPV)-based screening. The Australian National Cervical Screening Program (NCSP) was established in 1991, and currently recommends 2-year screening with

conventional cytology in ever sexually active women aged 18/20–69 years; it achieves participation rates of 58% and 83% over 2 and 5-year periods.¹ The implementation of the National HPV Vaccination Program in April 2007, however, prompted a review of the NCSP.

HPV vaccination in Australia is publicly funded and includes school-based vaccination of females and males aged 12–13 years with the quadrivalent HPV16/18/6/11 vaccine (CSL, Melbourne, Australia). Community-based catch-up vaccination in females up to 26 years was also implemented to the end of 2009. Australia's vaccination programme has a high level of three-dose coverage reported (approximately 73% in initial cohorts of 12–13-year-old girls and ~30%–50% in the older catch-up cohorts who were aged 20–26 years in 2007).^{2–4} A number of studies have now documented the effects of the vaccination programme in substantially reducing vaccine-included type-specific infections, anogenital warts and high-grade cervical abnormalities in young women in Australia.^{5–7}

In the postvaccination era, population-based cervical screening is still necessary; cohorts vaccinated with first generation HPV vaccines have only partial protection against cervical cancer because these vaccines target only HPV16/18. In addition, women vaccinated after exposure to HPV16 or 18 are still at risk for HPV16 and HPV18-related cervical cancer as vaccination does not alter the clearance of pre-existing HPV infections.⁸ However, as the vaccination status of the population targeted for screening varies over time and more vaccinated cohorts reach screening age, the reduction in prevalence of cervical lesions has potential to adversely impact the test performance characteristics of cytology screening,⁹ which has been tailored to detect the cytological manifestations of HPV infections.

Primary HPV testing has been reviewed and endorsed as a primary screening method by the International Agency for Research on Cancer.¹⁰ Results from international randomised controlled trials have shown that compared with cytology, primary HPV testing has an increased sensitivity for high-grade precancerous disease (cervical intraepithelial neoplasia grade 2 or more severe diagnoses; CIN2+) which, in an initial round of screening, results in increased detection of high-grade abnormalities.^{11–13} Consequently, in follow-up screening rounds, reduced rates of cervical intraepithelial neoplasia grade 3 (CIN3, adenocarcinoma in situ [AIS]), or invasive cervical cancer (CIN3+) have been observed. A major meta-analysis of data from four large European trials, involving pooled data on 276 000 women, found that as follow-up increased beyond 2–3 years, HPV testing resulted in up to 60% increased protection against invasive cervical cancer, compared with cytology-based screening.¹⁴ Observational studies also provide evidence of lower rates of CIN3+ in HPV-negative compared with cytology-negative women over time. For example, an analysis of pooled data in the Joint European Cohort Study found that the cumulative rate of CIN3+ in HPV-negative

women at 6 years after HPV testing was 0.27% (95% CI 0.12% to 0.45%) compared with the rate at 3 years for women who were cytology negative at baseline, which was 0.51% (95% CI 0.23 to 0.77).¹⁵

A number of clinical HPV tests have been developed. The first tranche of international randomised controlled trials used either Hybrid Capture 2 (QIAGEN NV, Netherlands) or consensus PCR based on GP5+/6+ primers, to test for any of a pool of 13 oncogenic HPV types at a clinically relevant analytical threshold.¹⁵ Subsequently, alternative HPV testing platforms emerged which are able to perform partial genotyping, that is, to stratify outputs for HPV-positive samples with respect to whether separate outputs are provided for the highest risk HPV types (HPV16/18 and/or other types). Of these alternative platforms, the cobas 4800 system was used in a major study of HPV screening in the USA (ATHENA)¹⁶ and findings from this study underpinned its approval by the US Food and Drug Administration in 2014 for primary screening in women aged over 25 years.

Various options have been proposed for the management of oncogenic HPV-positive women in the context of primary HPV screening. These include cytology triage, partial genotyping with direct referral of women who test positive for HPV16/18 to colposcopy, and use of dual staining (DS) of liquid-based cytology (LBC) preparations for molecular markers p16^{INK4a} (p16) and Ki-67 for triaging women in whom oncogenic HPV is detected.^{17–19} Partial genotyping, potentially in conjunction with the other approaches, appears to be a highly promising strategy for high-volume clinical testing with further risk stratification through the detection of HPV16 and HPV18, allowing the differential (more aggressive) management of women infected with the HPV types most often found in cervical cancer.²⁰

In an HPV16/18-vaccinated population, as in Australia, the prevalence of infections and related CIN2+ lesions is reduced in young women, and thus HPV screening generally, and partial genotyping strategies in particular, become more practical than was the case in unvaccinated populations. In Australia, screening is currently conducted starting at 18–20 years with cervical cytology and thus HPV screening involves starting at an older age than currently. In Australia, all women in the age group 25–34 years have been offered vaccination and thus infections in women <30 years are less prevalent than in the prevaccination era.

The implementation of prophylactic HPV vaccination in Australia, combined with mounting evidence of the increased protection provided by primary HPV screening in comparison to cytology-based screening, prompted a major review of the NCSP in 2011–2014, known as 'Renewal'. As part of the renewal process, the Australian Medical Services Advisory Committee (MSAC) commissioned a systematic review of the literature and effectiveness and economic modelling of 132 potential screening strategies, including cytology-based and HPV test-based strategies.^{21 22} Based on the findings of the review, in April

2014, MSAC recommended that the NCSP transition to 5-year primary HPV screening with partial genotyping for women aged 25–69 years, and LBC triage for women who test positive for oncogenic HPV other than 16/18, with HPV exit testing at 70–74 years of age. In 2015, the Australian Health Ministers' Advisory Council approved the draft policy for renewal of the NCSP, and in June 2015 the Department of Health of Australia commissioned the development of new clinical management guidelines.²³

The renewal has now entered an implementation phase, with full roll-out of the changes now planned for December 2017 (after an initial implementation delay). In the Australian context, reimbursement for HPV screening in the renewed NCSP will be through the Medicare Benefits Schedule (MBS). The MBS item descriptor specifies the conditions under which pathology will be reimbursed, and the new MBS item descriptor specifies that this will only occur after 57 months from a prior negative HPV test.

The investigator-initiated Compass trial was set up as a sentinel experience for the national programme with the view to inform processes and plan for the challenges of implementing the renewed programme. The main purpose of the trial is to evaluate and compare the performance of image-read cytology versus primary HPV screening in both vaccinated and unvaccinated women. The trial is conducted in two phases. Recruitment into the first phase (pilot study) was completed in November 2014 and follow-up will continue within the pilot for 5 years following recruitment. The aim of the current paper is to describe the design, objectives and processes involved in the second phase, the Compass Main trial. This paper summarises Version 1.6 of the trial protocol (October 2017).

METHODS AND ANALYSIS

Trial design and randomisation

Compass is a two-armed, open-label randomised trial coordinated at the Victorian Cytology Service (VCS). Participants will be randomised to (1) 2.5-year image-read LBC screening with reflex HPV triage testing for low-grade smears (atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesions) (control Arm A) or to (2) 5-year HPV screening with partial genotyping for HPV16/18 (intervention Arm B) (primary randomisation). Oncogenic HPV-positive women who tested positive for HPV16/18 will be referred directly to colposcopy while those oncogenic HPV-positive women who tested negative for HPV16/18 (ie, not 16/18) will be randomised to either triage with image-read cytology testing or dual-stained (DS) cytology testing (immunocytochemistry) for biomarkers p16 and Ki-67 (secondary randomisation). A schematic representation of both study arms is shown in [figures 1 and 2](#).

Primary randomisation to either Arm A or B will have a 1:2 (cytology:HPV) allocation ratio while secondary randomisation to either cytology or DS triage testing

will have a 1:1 allocation ratio. Randomisation will be performed remotely using an online system, via a computer-generated minimisation procedure, stratified by age at recruitment (date of birth (DOB) <1 July 1980 and DOB ≥1 July 1980), representing strata who were either age eligible or not age eligible for publicly funded HPV vaccination in Australia's National HPV Vaccination Program. The randomisation schedule and process is the responsibility of the National Health and Medical Research Council's (NHMRC) Clinical Trials Centre at the University of Sydney.

Neither the participant nor the recruiting practitioner will be aware of subject allocation at the time of recruitment. Randomisation will be performed upon receipt and logging of the enrolment cervical sample at VCS Pathology, and will not be concealed in the laboratory (for reasons of practicality). The recruiting practitioner will be notified of the randomised allocation and screening test results via a laboratory report which will include a recommendation for clinical management.

Overall, participants in Arm A (LBC screening) will experience three screening rounds (round 1 at baseline, round 2 at 2.5 years, and round 3 at 5 years) and participants in Arm B (HPV screening) will experience two screening rounds in the trial (round 1 at baseline and round 2 at 5 years). In addition, as part of safety monitoring follow-up, 10% of women in each stratum of the HPV screening arm in whom HPV is not detected will be recalled at 2.5 years for LBC testing.

Eligibility criteria

The trial inclusion criteria are:

- ▶ Female residents of Australia aged 25–69 years who are attending for routine cervical screening.
- ▶ Participants may also be in follow-up management for a previous abnormality or unsatisfactory cytology. Women may have been previously enrolled in the Compass pilot study but must have been discharged to routine screening.

Exclusion criteria include:

- ▶ Previous total hysterectomy (uterus and cervix).
- ▶ The presence of symptoms or signs for which cervical cancer must be excluded.
- ▶ Currently undergoing treatment for cervical cancer.
- ▶ Currently enrolled in the Compass pilot study.

Women who are pregnant or become pregnant during the trial will be eligible for enrolment. They will be managed according to trial protocol. Any subsequent colposcopy will be managed as per clinical management guidelines for pregnant women.^{23 24}

Recruitment

Potential participants will be identified by medical practitioners or nurses at one of the participating primary healthcare clinics or sexual health clinics. Recruiting practitioners will be shown how to obtain informed consent and the VCS liaison physicians will regularly liaise

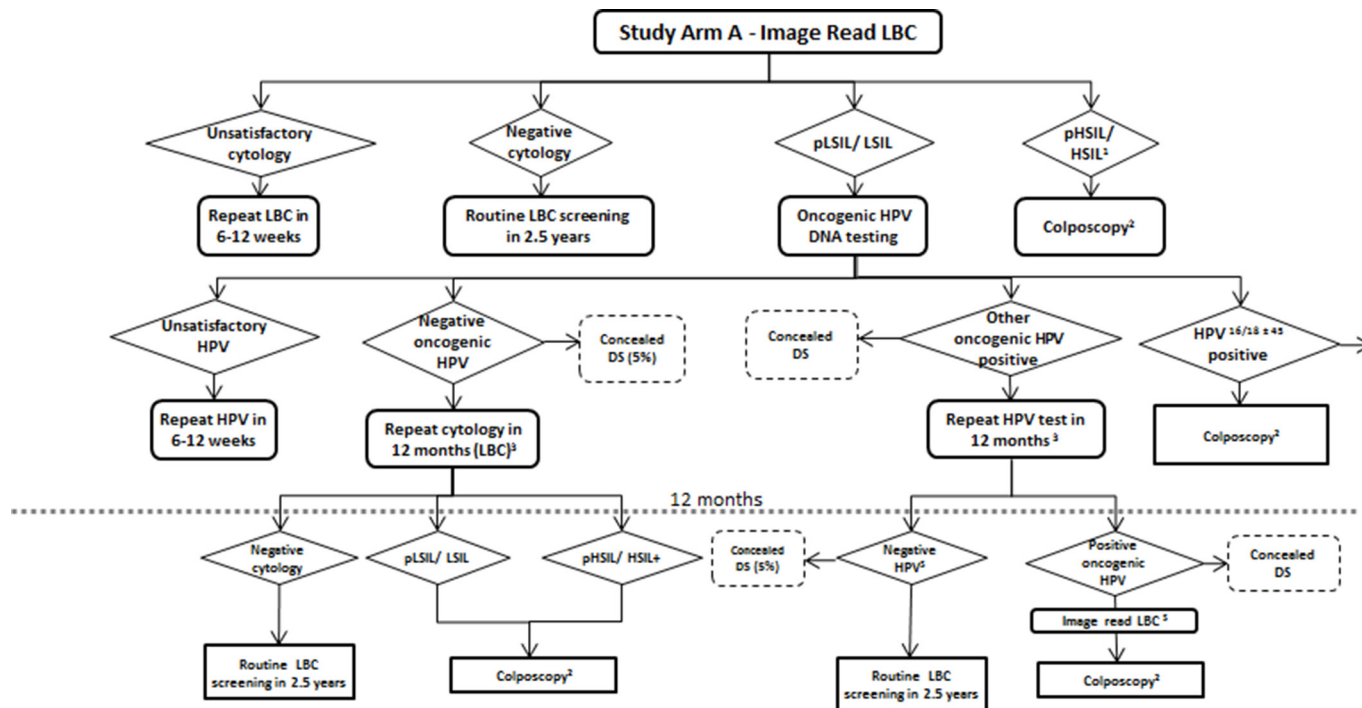


Figure 1 Flow chart of study Arm A, 2.5-year image-read, liquid-based cytology. DS, dual staining; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesions; pLSIL, Possible LSIL in the Australian Modified Bethesda System is broadly equivalent to ASCUS in US Bethesda system; pHSIL: Possible HSIL in the Australian Modified Bethesda System is broadly equivalent to ASC-H in US Bethesda system.¹ Includes any glandular abnormality, possible high-grade endocervical glandular lesions and atypical glandular cells of uncertain significance.²If results at colposcopy are negative/cervical intraepithelial neoplasia 1 (CIN1)/HPV, women require one negative follow-up test at 12 months, using index test, before returning to routine screening (return to original study arm). If CIN 2+/adenocarcinoma in situ (AIS): treatment and follow-up according to The NCSP guidelines. Colposcopy unsatisfactory: managed by the individual specialist, informed by The NCSP guidelines.³ AIS will have annual co-test (HPV and LBC) indefinitely. Refer to the NCSP guidelines, Chapter 11 Management of Glandular Abnormalities, Flowchart 11.4 follow up after excisional treatment for AIS.⁴ LBC result to assist colposcopy reading they do not feed into the recommended follow-up for women.⁵ Concealed dual stain not for management of women.

with practitioners throughout the duration of the trial to support compliance with the study protocol. The practitioner will decide whether the woman is able to make informed consent and if so, invite her to participate in the trial. Eligible women will be given an information sheet to read. If they choose to participate they will be provided with a consent form to read and sign and will have a routine cervical sample collected into an LBC phial. The LBC sample phial will be labelled and sent to VCS Pathology with the signed patient consent form. Each consent form will be scanned and stored electronically as part of the VCS Pathology laboratory record. Participants will be recruited until the recruitment targets are met for each of the prespecified age strata.

Screening and triage test technologies

Samples in the trial will be collected using the PreservCyt/ThinPrep (Hologic, MA, USA) sample medium. Image-read LBC analysis will be carried out using the Hologic ThinPrep Imaging System. HPV DNA testing will be performed using the cobas 4800 HPV technology (Roche Molecular Systems, Pleasanton, CA, USA) incorporating the sample preparation kit (c4800 SMPL PREP), the

amplification/detection kit (c4800 HPV AMP/DET), the preparation kit (c4800 LIQ CYT) and the wash buffer kit (c4800 WB). For dual-stained cytology testing, CINtec PLUS DS technology that stains for p16 and Ki-67 markers (Ventana Medical Systems, AZ, USA) will be used. The devices mentioned above are listed on the Australian Register of Therapeutic Goods and will be used within their listed approved use.

Procedures and follow-up processes

VCS operates VCS Pathology, the Victorian Cervical Screening Registry, the South Australian Cervix Screening Registry and the National HPV Vaccination Program Register. All cytology and HPV DNA testing will be performed at VCS Pathology by trained staff and according to the relevant manufacturer's instructions. Prealiquots will be taken before sample testing for future testing with different HPV testing technologies, as per consent form. The laboratory report issued to the practitioner from VCS Pathology will specify an overall cervical screening result (low, intermediate or higher risk for cervical cancer or precursors, or unsatisfactory), the primary test performed and its result, any reflex test

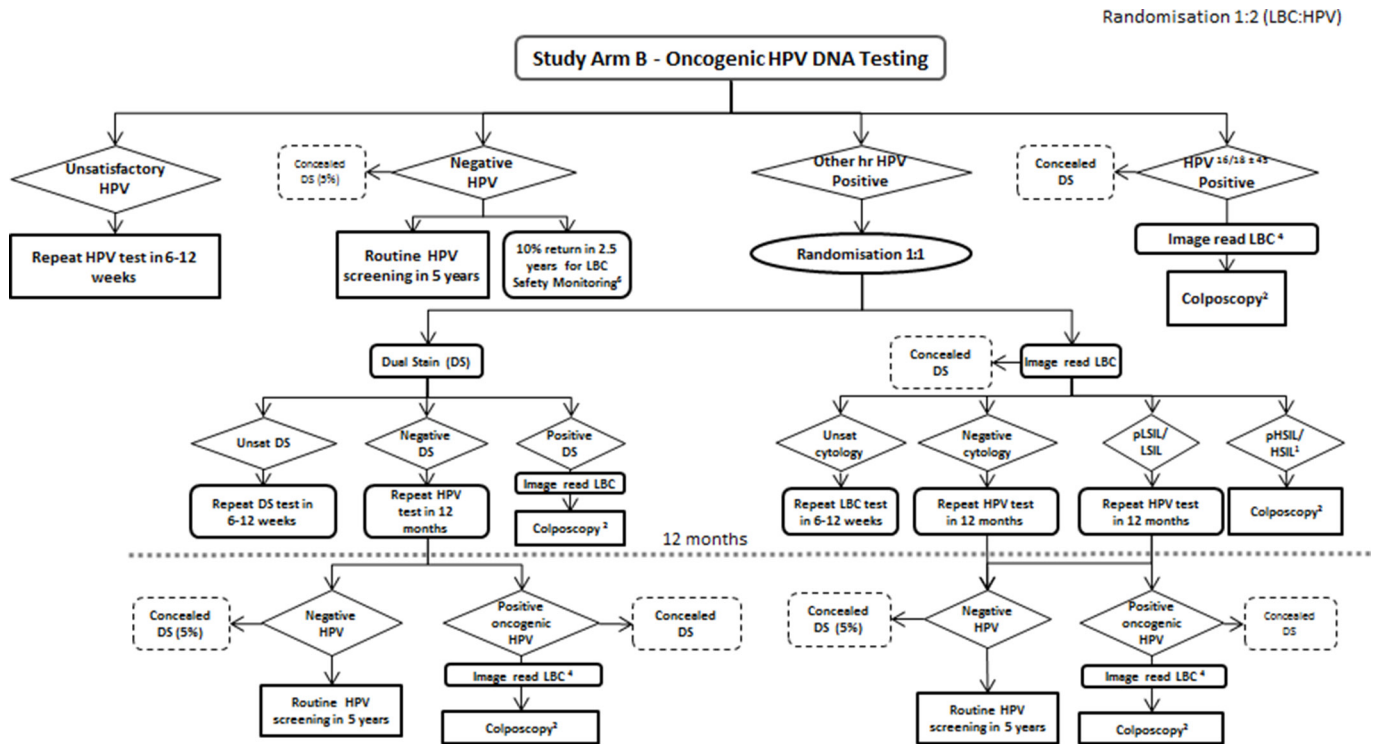


Figure 2 Flow chart of study Arm B, 5-year primary HPV testing with partial genotyping. HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesions; pLSIL: Possible LSIL in the Australian Modified Bethesda System is broadly equivalent to ASCUS in US Bethesda system; pHSIL: Possible HSIL in the Australian Modified Bethesda System is broadly equivalent to ASC-H in US Bethesda system; unsat, unsatisfactory.¹ Includes any glandular abnormality, possible HG endocervical glandular lesions and atypical cells of uncertain significance.² If results at colposcopy are negative/CIN1/HPV, women require one negative follow-up test at 12 months, using index test, before returning to routine screening (return to original study arm). If CIN 2+/AIS: treatment and follow-up according to The NCSP guidelines. Colposcopy unsatisfactory: managed by the individual specialist, informed by The NCSP guidelines.³ AIS will have annual co-test (HPV and LBC) indefinitely. Refer to the NCSP guidelines, Chapter 11 Management of Glandular Abnormalities, Flowchart 11.4 follow up after excisional treatment for AIS.⁴ LBC result to assist colposcopy reading they do not feed into the recommended follow-up for women.⁵ Concealed DS not for management of women.⁶ Configurable randomisation—may be adjusted during the trial.

performed and its result and, finally, a recommendation for clinical follow-up that takes account of the woman's screening history and the current results (according to the flow charts in figures 1 and 2). A purse-sized reminder card with the woman's name and the date when the next test is due will be made available to participants either via the practitioner or directly mailed to the woman where her practitioner does not routinely receive hard copy laboratory results.

Women will be followed through cervical screening registers which routinely provide a safety net to support the follow-up of screen-detected abnormalities through contact with practitioners and women where appropriate follow-up is apparently overdue. Invitations for routine rescreening tests will be sent by the VCS, 3 months prior to the due date in order to support adherence to the specified screening interval in each study arm. Reminder letters will be sent to participants who do not attend within 3 months. To address the longer screening intervals, in addition to established registry procedures, the register will attempt to make contact by mobile phone and/or email (where these details have

been provided by the woman at enrolment) with women who cannot be reached through the usual follow-up processes.

For women referred for diagnostic evaluation, any histopathological evaluation will be performed by the pathology laboratory routinely used by the colposcopist. As per normal clinical processes, the pathologist providing the original report will be aware of the findings of the screening and triage tests and other relevant clinical information. All clinical management will be based on the results of routine clinical analysis. Women diagnosed with cervical cancer will undergo usual care, as appropriate. Currently, p16 immunohistochemistry testing for histopathology is not conducted consistently, but this is now recommended when the pathologist believes that the lesion represents CIN2, under the recently released Royal Australasian College of Pathology structured reporting protocol for preinvasive cervical neoplasia which incorporates the lower anogenital squamous terminology recommendations.²⁵ Thus, the local histology reading processes for Compass participants will not be standardised with respect to the use of p16 staining.

To support the analysis of the primary and secondary trial outcomes, a second histopathology analysis will be performed at a later date by an independent quality control (QC) panel comprising three non-local expert pathologists who will be blinded to the source of the slides. They will perform QC review on all biopsies taken, with discordant results defined as a result for which the colposcopy-directed biopsy does not correlate with the LBC done at the time of referral to colposcopy. The QC histology reading will be done both with and without p16 immunohistochemistry testing. The trial outcomes will be reported against all three reference standards (local histology, and QC histology with and without p16 testing). However, it should be noted that the main endpoint for analysis will be based on histologically confirmed CIN3+ according to QC histopathology but not including reclassified CIN2 which is p16 immunohistochemistry positive. In addition, the QC reference standard which does not include p16 assessment will also provide an uncorrelated assessment of the performance of dual-stained cytology (which involves p16) as a triage test of HPV-positive women, for the related secondary endpoints.

For women in whom the QC histopathology analysis indicates a previously undiagnosed CIN2/3+ lesion, their primary practitioner will be made aware of the QC diagnosis (although it should be noted that this QC diagnosis may be performed several years after the local diagnosis). If the woman has not been referred for further evaluation or for treatment of high-grade cervical precancerous disease since the biopsy in question was originally taken, the letter to the practitioner will recommend that further investigation is conducted and that treatment of a confirmed high-grade lesion proceeds according to the appropriate clinical management guidelines, which after the implementation of the renewed NCSP will involve the new 2017 NCSP guidelines.²³

Compass participants who are treated for CIN2+ disease will have post-treatment follow-up according to existing NCSP guidelines including 'test of cure' (ie, the use of follow-up testing for surveillance of any recurrence which generally involves cotesting with HPV and LBC).²³ These women will be passively followed up via the register for a 5-year follow-up period. Following completion of test of cure follow-up and surveillance, these women will return to routine screening in accordance with the appropriate national clinical management recommendations.

Primary outcomes, statistical design and sample size calculations

The primary trial outcome is the assessment of cumulative CIN3+ (including CIN3 and invasive cervical cancer) at 5 years, following a 5-year HPV exit test round in both arms, in women randomised to the HPV arm versus women randomised to the LBC arm, on an intention-to-treat (ITT) basis.

The primary analysis will be unadjusted and will be performed on an ITT basis using Kaplan-Meier estimates. The primary outcome will first be tested for non-inferiority,

and if non-inferiority is declared the primary outcome will be tested for superiority. This testing procedure is commonly known as closed loop testing. Assuming a total average CIN3+ rate in the LBC arm (across unvaccinated and vaccinated women) of 0.6%, and an absolute non-inferiority margin of 0.22%, the trial will have >90% power with 97.5% confidence to detect non-inferiority for the HPV arm, allowing for a 10% non-compliance rate. This sample is adequately powered to detect this margin should the LBC rates be higher than the assumed 0.6%. The non-inferiority comparison will be one sided and all other comparisons will be two sided. All comparisons will use a 0.05 level of significance.

A total of 36 300 women in the birth cohorts not offered vaccination and 84 700 women in the cohorts offered vaccination will be recruited, bringing the final sample size to 121 000. Of these, 7700 women will be recruited for a safety monitoring sample (10% of HPV screen-negative participants presenting for routine screening). Those presenting for routine follow-up (approximately 5%) will be assigned to the management branch of the arm to which they will be randomised. These women, however, will not be included in the analysis for the primary outcome.

A major impact of this study will be the value of extended screening intervals in patients who are screen negative at baseline. Logistically, it would be difficult to randomise patients after baseline screening and as such, the cumulative 5-year CIN3+ rates in baseline screen-negative patients may no longer be strictly comparative. However, this is a critical scientific question and so the sample size for the trial is powered for the secondary outcome of cumulative CIN3+ assessment in screen-negative women, adjusted for censoring after CIN2+ treatment and adjusted for hysterectomy. Therefore, analysis will be performed of cumulative CIN3+ in women presenting for routine screening randomised to the HPV arm who were HPV negative at baseline versus CIN3+ in those randomised to the LBC arm and who were LBC negative at baseline, adjusted for censoring after CIN2+ treatment and after hysterectomy and stratified by recruitment group (DOB \geq 1 July 1980 and $<$ 1 July 1980). ITT analysis will be performed with closed loop testing for non-inferiority and superiority if non-inferiority is declared. Per-protocol analysis for this critical secondary outcome will also be performed in women screened and followed up within a defined tolerance period.

For this critical secondary outcome, the sample size for women not offered vaccination was based on estimated CIN3+ rates at 5 years in women who test cytology negative and HPV negative at baseline (round 1) of 0.48% and 0.26%,²⁶ estimated rates of negative cytology tests at baseline of 90.8% (VCCR 2012, unpublished data) and a loss to follow-up rate of 5% in each arm. For women who were offered vaccination, the sample size was based on an estimated three-dose vaccination coverage of 75% and an estimated overall population-level vaccine effectiveness of 70% (from a specific modelled analysis to

support these estimates), estimated CIN3+ rates at 5 years in women who test cytology negative and HPV negative at baseline (round 1) of 0.23% and 0.12%, estimated rates of negative cytology tests at baseline of 82% (VCCR 2012, unpublished data) and a loss to follow-up rate of 5% in each arm.

Participants with no ascertained histological outcomes at the end of the trial (including participants who fail to attend their exit test within the required time frame, participants with a negative exit test and participants with a positive exit test who fail to attend any recommended follow-up tests within the required time frame) will be classified as not having detected CIN2+ for the purposes of the analysis.

Incidence rates of adverse events, including deaths and stage Ia2+ invasive cervical cancers, will be reported over the whole study period.

All analyses will be conducted on deidentified data at the Cancer Research Division of Cancer Council NSW (CCNSW).

Secondary and supplementary outcomes

A number of secondary outcomes have been planned as summarised in [table 1](#). These outcomes will be assessed separately in cohorts of women not offered HPV vaccination and in cohorts who were offered vaccination (born ≥ 1 July 1980). As described above, a critical secondary outcome will involve cumulative CIN3+ inscreen-negative women at the baseline round, who were in routine screening at the time of enrolment. This will be done on an ITT basis and a per-protocol basis. The strict per-protocol criteria will involve: women randomised to LBC, who had an LBC test in months 27–39 from the date of the original invitation to attend screening (which may be up to 3 months before attendance) and then who had HPV exit testing at trial exit from 57 to 69 months after recruitment; and women randomised to HPV testing, who did not have an intermediate cytology screen until HPV exit testing at 57–69 months (except in the case of the safety monitoring group). Analysis assuming progressively less strict per-protocol adherence criteria will also be performed.

Exploratory subgroup analyses will be performed using baseline variables including age, country of birth (with a focus on Australian born vs not Australian born), language spoken at home (English vs not English) and screening history. Regression models will be constructed to examine the association of any baseline factors with CIN3+ and CIN2+ outcomes. In this pragmatic trial, participants will be passively followed up through the cervical cancer screening registry and participants with inconclusive tests will be recalled for a repeat test as specified in the management flow charts.

A number of supplementary analyses will be performed as follows.

Compass biobank

Participants will be explicitly asked to consent to their samples being used for biobanking. All samples from

screen-positive women will be stored, and a random sample of screen-negative women will be stored after the baseline screening round. A similar sampling procedure will be used at the 2.5-year screening round for the cytology arm and HPV safety monitoring, and at the 5-year HPV exit testing round. A biobank will be created for research purposes by storing residual samples from consenting women, and for additional retrospective testing of alternative test technologies which will not be used to manage women in the trial. Residual samples in LBC phials will be stored for a minimum of 1–3 months according to usual laboratory practices and at a later time, cell pellets may be spun down and frozen as whole cells, allowing for assessment of DNA, RNA or protein biomarkers. This biobank resource will comprise population-based samples which, after ethical approval, will have capacity to be linked to the results of histopathology analysis, screening test history, trial outcomes and other data.

Screening-related harms

It is important to assess the harms as well as the benefits of screening. Screening-related harms generally relate to the potential for overdiagnosis and overtreatment. As a measure of the harms of alternative screening approaches, we will assess colposcopy referral rates and treatment rates, which will enable us at the end of the trial to calculate measures for number-needed-to-colposcopy and number-needed-to-treat to prevent each CIN3+. Quality-of-life assessment is also planned in a subgroup of participants (the Compass-Plus study - see below for more detail).

Performance of dual-stained cytology versus LBC as a triage test

Based on pilot study results,²⁷ we expect that after 1-year follow-up for triage-negative women and subsequent referrals are taken into account, the performance of LBC (at a pHSIL/ASC-H threshold) and DS to detect CIN2+ in women with other high-risk (OHR) HPV will be broadly comparable. However, DS is expected to improve immediate detection of CIN2+ and thus minimise loss to follow-up at 12 months, thus increasing CIN2+ detection overall within a 'real world' screening programme.

We will use closed loop testing, and if non-inferiority is satisfied we will test for superiority for immediate detection of CIN2+ in the DS versus the LBC group. Analysis will be stratified by age eligibility for vaccination. About 24 200 participants not eligible for HPV vaccination will be randomised to the HPV arm. Of these, approximately 22 290 (95%) will be in routine screening at recruitment and about 784 (3.4%) of these will test OHR HPV positive. Assuming an immediately detected CIN2+ rate of 8.2% in the LBC triage arm (based on pilot study results), and an absolute non-inferiority margin of -5.5%, the trial will have 80% power with 97.5% confidence to detect non-inferiority for the DS triage subarm. About 56 468 participants eligible for HPV vaccination will be randomised to the HPV arm. Of these, approximately 53 645 (95%) will be in routine screening at recruitment and about 7548

Table 1 Secondary trial outcomes

Description of secondary outcomes	Time point	Additional notes
Cross-sectional outcomes for CIN2+ and CIN3+ detection in each arm	Baseline, following recruitment	Analyses will be stratified by recruitment group (DOB <1 July 1980; DOB ≥1 July 1980).
CIN2+ in women randomised to the HPV arm and positive for other oncogenic HPV types (not 16/18)	After completion of 12–24m FU	Analyses will be stratified by recruitment group (DOB <1 July 1980; DOB ≥1 July 1980).
Cumulative CIN3+ in women randomised to HPV arm who were HPV negative at baseline versus cumulative CIN3+ in those randomised to LBC arm who were LBC negative at baseline using ITT analysis	After completion of FU at 5 years	Closed loop testing for non-inferiority and superiority if non-inferiority is declared. Analyses will be adjusted for censoring after CIN2+ treatment or after hysterectomy and stratified by recruitment group (DOB <1 July 1980; DOB ≥1 July 1980).
Cumulative CIN3+ in women randomised to HPV arm who were HPV negative at baseline versus cumulative CIN3+ in those randomised to LBC arm who were LBC negative at baseline and at 2.5 years. Per-protocol analysis will be performed in women screened and followed up within a defined tolerance period. The strict per-protocol criteria will involve: (1) women randomised to LBC, who had an LBC test in months 27–39 from the date of the original invitation to attend screening (which may be up to 3 months before attendance) and then HPV exit testing at trial exit from 57 to 69 months after recruitment; (2) women randomised to HPV testing, who did not have an intermediate cytology screen until HPV exit testing at 57–69 months (except in the case of the safety monitoring group). Analysis assuming progressively less strict per-protocol adherence criteria will also be performed.	After completion of FU at 5 years	Analyses will be adjusted for censoring after CIN2+ treatment or after hysterectomy and stratified by recruitment group (DOB <1 July 1980; DOB ≥1 July 1980).
Cumulative CIN2+ in women randomised to the HPV arm who were HPV negative at baseline versus cumulative CIN2+ in those randomised to the LBC arm who were LBC negative at baseline LBC arm and using intention-to-treat analysis	After completion of FU at 5 years	Analyses will be adjusted for censoring after CIN2+ treatment or after hysterectomy and stratified by recruitment group (DOB <1 July 1980; DOB ≥1 July 1980).
Cumulative CIN2+ and CIN3+ in women who have an abnormal test result at baseline	After completion of FU at 5 years	Analyses will be adjusted for censoring after CIN2+ treatment or after hysterectomy and stratified by recruitment group (DOB <1 July 1980; DOB ≥1 July 1980).
Cumulative CIN2+ and CIN3+ in women who were in follow-up management for a previous abnormality at baseline	After completion of FU at 5 years	Analyses will be adjusted for censoring after CIN2+ treatment or after hysterectomy and stratified by recruitment group (DOB <1 July 1980; DOB ≥1 July 1980).

CIN, cervical intraepithelial neoplasia; DOB, date of birth; FU, follow-up; HPV, human papillomavirus; ITT, intention to treat; LBC, liquid-based cytology.

(14.1%) of these will test OHR HPV positive. Assuming an immediately detected CIN2+ rate of 5.0% in the LBC triage subarm (based on pilot study results), and an absolute non-inferiority margin of -1.5%, the trial will have more than 80% power with 97.5% confidence to detect non-inferiority for the DS triage subarm.

Long-term outcomes

Pending ethical and data custodian approvals, long-term outcomes will be examined in all participants, including outcomes at 10 and 20 years postrecruitment (although women will return to routine screening practice after 5-year exit testing). Women will be passively followed over time using registry data for long-term outcomes for CIN2+ and CIN3+, and invasive cervical cancer. This will be done for a number of subgroups including women who cease screening at different ages, women who start screening at different ages and women in broad age strata who have different patterns of screening behaviours (eg, regular 5-year screening vs irregular screening or under-screening). We will also assess outcomes in women who access self-collected HPV testing after trial exit as part of the renewed HPV-based cervical screening program in Australia.

Demographic, lifestyle and quality-of-life substudy (Compass-Plus)

Pending specific ethical approval, we will approach a subgroup of participants for their consent to participate in Compass-Plus, which will involve a self-administered questionnaire at baseline and at each follow-up point in a subgroup of participants. This will facilitate a range of supplementary analyses which will include assessing the demographic and lifestyle factors associated with screening participation and outcomes, and vaccination status, as well as assessing quality-of-life issues. Compass-Plus will include a longitudinal study of health state utilities (quality-of-life benefit) related to the screening and follow-up management experience.

Anticipated recruitment and analysis timing

Recruitment for the pilot study began in 2013 and the recruitment target was met in late 2014. Recruitment for the main trial began in January 2015 and the target of 121 000 participants is anticipated to be attained in 2018. Final timing of analysis will be contingent on timing of recruitment in each arm. The timing for each planned analysis accounts for an additional period of 9 months added to allow for 3 months' follow-up delay and 6 months to obtain histology outcomes.

For participants who were not age eligible for HPV vaccination, baseline analysis (including 12-month follow-up of those managed via 12-month surveillance) will be conducted in approximately January 2018. Analysis for the 2.5-year screening round (Arm A) and 2.5-year safety monitoring analysis (Arm B) is planned for July 2019, and analysis for the final 5-year outcomes is anticipated in early 2022. For participants who were age eligible for HPV vaccination, baseline analysis (including 12-month

follow-up) for a subset for which sufficient follow-up is available is anticipated in approximately January 2018. Final baseline screening round analysis is anticipated in 2019–2020. The 2.5-year screening round (Arm A) and the 2.5-year safety monitoring analysis (Arm B) are anticipated in 2021–2022, and the final 5-year outcome analysis is expected in 2023–2024. Thus, the estimated trial completion date is 2024 although as noted long term passive follow-up through registries will also be conducted, pending ethical approval for such follow-up.

Data collection and management

Databases at VCS Pathology and the registers will store individual participant screening results and follow-up data for the Compass trial as part of routine medical record management. In the screening programme, all cervical cytology, histology and HPV test results are routinely forwarded to the registers from the reporting laboratory, along with identifying information for the purposes of reminders and follow-up, unless a woman chooses to opt off. As part of the trial, the registers will provide information on DOB, local government area, cervical screening episodes and results of care delivered within the screening programme to investigators at CCNSW in a deidentified but record-linked format. In addition, participants will also be followed up via linkage to a number of other routinely collected data sets which will be undertaken with the informed consent of participants and following approvals from data custodians and ethics committees. Linkage will be made to the National HPV Vaccination Program Register for information on vaccination status, doses delivered and timing of vaccination; to Medicare Australia for address information as a fail-safe for women otherwise lost to follow-up; to state-based cancer registries for confirmation of cervical cancer or cancer-free status and to state-based Registries of Births, Deaths and Marriages for confirmation of vital status.

VCS has well-established documented policies and procedures to cover operations in both technical and non-technical areas of VCS Pathology, Victorian Cervical Cytology Registry (VCCR) and the National HPV Vaccination Program Register. VCS Pathology is a specialist gynaecological pathology laboratory which fully complies with AS ISO 15189:2009 (international standards), NATA (National Association of Testing Authorities, Australia) and NPAAC (National Pathology Accreditation Advisory Council, Australia) standards relevant to its scope of activities. VCS Pathology has an established staff training and continuing professional development programme, and an ongoing competency assessment of staff, and undergoes regular internal auditing (including for Compass) as part of NATA accreditation.²⁸ HPV positivity and unsatisfactory rates, as tested on two Roche cobas 4800 instruments, will be reported each week to the Compass meeting for the purposes of tracking quality, and unsatisfactory samples will be investigated to determine the cause, where possible. All instruments will be tested for accuracy as part of an ongoing national quality assurance

programme (Royal College of Pathologists of Australasia—RCPA QAP). In terms of data quality, in addition to standard laboratory practices required by NATA, an audit of 10% of Compass Main trial request forms will be undertaken.

Participants will be assigned a unique study ID code at the VCS. Data will be extracted in a deidentified format on a regular basis from the registers and stored on secure servers accessed only by authorised trial personnel. Data will be securely transferred between the registers and CCNSW via a secure web-based portal or using password-protected disks/memory sticks. Data will be stored in electronic format on secure network computers for use during the duration of the research project. Access to electronic data files will be restricted to those directly involved in the study on password-protected computers located at CCNSW.

CCNSW's authorised staff will maintain the study database and perform statistical analysis. No personal information identifiers will be stored in the analysis file; all identifying information will be removed from data sets and replaced with a numeric code. A master list linking numeric codes to identifying information will be stored at the VCS, and thus a woman will be able to be identified by VCS if the analysis by CCNSW determines there is a safety monitoring issue or inconsistency in the data.

Compass data, files and study operating procedures will be monitored regularly, and reviewed annually by the project coordinator to ensure the trial procedures comply with the approved protocol and Human Research Ethics Committee (HREC) requirements.

ETHICAL CONSIDERATIONS, SAFETY MONITORING AND DISSEMINATION

Ethical approval

The Compass protocol and all trial documents have been reviewed and approved by the Bellberry Human Research Ethics Committee (2014-11-592) (lead ethics committee) and the Royal Australian College of General Practitioners, National Research Evaluation and Ethics Committee (NREEC 15-003). Both ethics committees operate within the NHMRC's National Statement on Ethical Conduct in Human Research (2007).²⁹ The trial will be conducted in compliance with the approved trial protocol and in line with the 2007 National Statement on Ethical Conduct in Human Research. No deviation from the protocol will be executed without the prior review and approval of the lead ethics committee. Any unanticipated necessary deviation from protocol will be immediately reported to the leading HREC according to its standard policies and procedures.

Safety monitoring

An Independent Data Safety and Monitoring Committee (IDSMC) composed of an independent group of experts has been configured to monitor the safety and efficacy of the interventions being investigated in the trial as well as monitoring the overall conduct of the trial to ensure the

study is of high quality. The IDSMC will review trial safety approximately every 6 months and provide recommendations including participant safety, recruitment and retention; protocol amendments; reporting of adverse events and ongoing trial conduct.

During the study, the investigators, practitioners and other site staff will be responsible for detecting and recording events, when they occur, meeting the criteria and definition of an adverse event or serious adverse event. Since cytology in the trial control arm (Arm A) is not performed according to current practice, events in this arm will also be monitored. In each arm, a number of outcomes will be monitored—these include deaths and invasive cervical cancer (stage 1a2+) to ensure that cumulative rates are not higher than expected population rates. The IDSMC will also be monitoring rates of CIN2+ detected in the baseline screening round, and assessing any invasive cervical cancers detected at baseline (note that these represent a success of the screening round rather than a failure). Therefore, both the cytology and the HPV-screened women will be continuously monitored for a number of safety outcomes.

In addition, 10% of women in each stratum of the HPV screening arm who test negative will be allocated to safety monitoring follow-up. At the point of allocation to this safety monitoring arm, women will be notified via the laboratory report that they will undergo LBC testing at 2.5 years. Follow-up of any abnormalities detected in safety monitoring will be conducted according to management recommended for study Arm A (figure 1).

Therefore, the safety monitoring outcomes overseen by the IDSMC include reported adverse events, stage 1a2+ invasive cervical cancers (stage 1a1 cancers will be excluded because they are screen detected), CIN2+ events and deaths in each group. The formulation of the stopping guidelines assumes that the age distribution of the participants in the Compass is equivalent to that observed in the general cervical screening population in the state of Victoria.

Dissemination of results

The findings of the trial will be reported in a series of papers in peer-reviewed journals and presented at national and international scientific forums. Results will be authored by study investigators, CCNSW and VCS study personnel. Findings will be published in statistical aggregate form so that no individual subjects are identifiable directly or indirectly. In addition to updates on the Compass website, dissemination of results to the lay public will be conducted via newspaper articles and radio interviews.

DISCUSSION

Before implementing the Compass trial, 5001 women were recruited to Compass pilot, which was conducted from 29 October 2013 to 7 November 2014. The objectives of the pilot were: (1) to assess participant acceptance of the randomisation process and use of longer routine

screening intervals; (2) to confirm the operational feasibility of laboratory processing procedures for HPV test platforms; (3) to assess test positivity rates for the primary screening test in each arm; and (4) to estimate the sensitivity and specificity of dual-stained cytology testing in women positive for HPV. Findings from the pilot indicate that the laboratory and referral procedures are practical and that women can be successfully enrolled into a trial of this nature, with the recruitment rate at most participating practices exceeding 50%. Analysis of pilot study data has also shown that primary HPV screening is associated with increased detection of high-grade cervical abnormalities compared with cytology, providing the first evidence in support of implementing primary HPV screening in a population with high uptake of the HPV vaccine.²⁷

It should be noted that the Compass trial does have some limitations. First, the study findings for women under 35 years are likely to be specific to populations which have experienced a high uptake of HPV vaccination, as has been the case in Australia. Additionally, the protocol for primary HPV screening (and also the protocol for HPV triage in the cytology screening arm) involves the use of next-generation HPV testing platforms which perform partial genotyping—referral of HPV16/18 positive direct to colposcopy is expected to improve the overall performance of HPV testing, but these HPV testing platforms may not be universally used in all countries. However, Compass will provide critical new information in terms of overall effectiveness of partial genotyping strategies in prevention of CIN3+ development longitudinally. This management strategy is expected to increase the overall effectiveness of primary HPV screening—and thus should impact (further reduce) the subsequent detection of CIN3+ after a negative HPV test. To our knowledge, Compass will be the first trial to assess cytology against HPV screening with partial genotyping using a prospective randomised design (as opposed to testing all women with both cytology and HPV). Partial genotyping represents the new ‘standard practice’ in HPV screening, and the large majority of clinical platforms now offer this option. This is in contrast to the systems used for the majority of the worldwide trials, initiated a decade or more in the past, which used either HC2 or GP5+/6+ testing, without specific partial genotyping.

‘Extended partial genotyping’ strategies which specifically test for, and directly refer, women with more HPV types (eg, types 31, 33 and/or 45) are potentially also of some interest. However, in an HPV16/18-vaccinated population, the current strategy is specifically designed to detect vaccine-included types for those cohorts now attaining screening age. Without the impact of vaccination to reduce prevalence of the types for which specific detection is followed by colposcopy referral, higher (and potentially unmanageable) rates of colposcopy referral would be expected in younger women. The trial can only assess a very limited number of the dozens of potential strategies (as for any trial)—in this case our focus is on the approach used for the renewed NCSP in Australia.

However, our approach is supported by an extensive review of the evidence and modelling of long-term outcomes.²²

Compass has a number of key strengths. It is a pragmatic study to be conducted under ‘real life’ conditions within the NCSP; it has long follow-up and uses technologies that have been widely used and have undergone quality assurance. Compass will be the first international study (to our knowledge) to evaluate the performance of each screening approach in both vaccinated and unvaccinated women. Also, for the first time within the context of cervical screening, women randomised to the primary HPV test arm will be stratified for differential management according to their risk of developing high-grade CIN based on partial genotyping and DS test results.¹⁶ Findings from the Compass trial will inform the implementation of the renewed NCSP in Australia planned for December 2017 and will also be relevant to countries transitioning from cytology-based screening to primary HPV screening in the context of HPV vaccination.

It is anticipated that next-generation nonavalent HPV vaccine, recently approved for use within the Australian vaccination program from 2018 onwards, will, in the long term, further change the paradigm for cervical screening. In Australia, this will take 12–13 years to have any impact due to the delay between routine vaccination of 12–13-year-olds and the new age of starting screening (25 years). In countries which continue to delay the age of starting screening to 30 years or longer, the implications are even longer term. Modelling of this much longer term issue suggests that in cohorts offered next-generation nonavalent vaccines, cervical screening will continue to be cost-effective, but that only a few screens per lifetime may be required.³⁰

Compass is designed to provide confirmation of the modelled findings which supported the transition to an HPV-based screening programme in Australia.²² This will form a ‘virtuous circle’—the trial will enable modelled predictions to be validated, and if necessary the detailed predictions can be updated to take into account actual behaviours in the new screening programme, vaccine coverage and other assumptions that were made in the original modelled analysis. This continuous improvement approach is in line with best practice modelling.³¹

In conclusion, Australia is a key first experience for screening in vaccinated populations. Therefore, although the data from the Compass trial may not yet be relevant to some countries, it will have inevitable implications as HPV-vaccinated cohorts age and enter the age range of screening. In some countries, where vaccination catch-up was to a more restricted age and where screening may start later (eg, >30 years), this trial will be of future relevance when vaccination cohorts start screening. Within a decade, the findings of the trial are likely to be highly relevant to the majority of developed countries and will thus provide a critical evidence base as countries plan the transition of cervical screening programme in the era of HPV vaccination.

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Contributors KC and MS developed the rationale for the trial and are coprincipal investigators. KC conceived the initial concept of the trial, led the development of the trial protocol and drafted the manuscript. MS and JDB have contributed to the trial protocol and operational procedures and processes at the VCS Ltd. PEC, VG and MC have been involved in the statistical design of the trial and the development of the trial protocol. SH has contributed to the design of study materials and coordinates the enrolment of practitioners and clinics. JDB is the clinical trial coordinator.

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Competing interests KC is co-principal investigator of Compass and JDB and MC (project coordinator, project statistician) are on the Compass study team. Compass is conducted and funded by VCS Ltd, a government-funded health promotion charity. Neither KC, JDB, MC nor their institution on their behalf (Cancer Council NSW) receives any direct funding from industry for this trial or any other project. MS (coprincipal investigator), JB and SH report that their institution, VCS Ltd, received equipment and funding from Roche Molecular Systems and Roche Tissue Diagnostics, AZ, USA, during the conduct of the study. PEC reports personal fees and non-financial support from Roche Molecular Systems, outside the submitted work. VG has no conflicts of interest to disclose.

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Title:

Protocol for Compass: a randomised controlled trial of primary HPV testing versus cytology screening for cervical cancer in HPV-unvaccinated and vaccinated women aged 25-69 years living in Australia

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